ORIGINAL ARTICLE BACTERIOLOGY

# Asymptomatic rectal carriage of *bla*$_{KPC}$ producing carbapenem-resistant Enterobacteriaceae: who is prone to become clinically infected?

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## Abstract

Carbapenem-resistant Enterobacteriaceae (CRE) are emerging extremely drug-resistant pathogens; *bla*$_{KPC}$ is the predominant carbapenemase in Israel. Early detection of asymptomatic rectal carriers is important for infection control purposes. We aimed to determine who among newly identified CRE rectal carriers is prone to have a subsequent clinical specimen with CRE. A matched case-control study was conducted in a tertiary care teaching hospital in Israel. Cases with a primary positive CRE rectal test and subsequent CRE clinical specimens were matched in a 1:2 ratio with CRE rectal carriers who did not develop subsequent CRE clinical specimens (controls). Matching was based on calendar time of primary CRE isolation, whether the primary CRE isolation was ≤48 h or >48 h after hospital admission, and time at risk to have a subsequent clinical specimen. Data were extracted from the patients' medical records and from the hospital's computerized database. One hundred and thirty-two newly identified CRE rectal carriers (44 cases, 88 controls) were included. The median time interval between screening and subsequent clinical specimens was 11 days (range, 3–27); 86% of the clinical specimens were classified as true infections. Independent predictors of subsequent CRE clinical specimens were: admission to the intensive care unit, having a central venous catheter, receipt of antibiotics, and diabetes mellitus. Identification of the risk factors for subsequent infections among CRE-colonized patients can be used to control modifiable risk factors and to direct empirical antimicrobial therapy when necessary.

**Keywords:** carbapenem-resistant Enterobacteriaceae, infection, Klebsiella pneumoniae carbapenemase, rectal carriage, risk factors
**Original Submission:** 19 January 2012; **Revised Submission:** 20 March 2012; **Accepted:** 29 March 2012
Editor: M. Paul
**Article published online:** 6 April 2012
*Clin Microbiol Infect* 2013; **19:** 451–456
10.1111/j.1469-0691.2012.03888.x

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## Introduction

Carbapenem-resistant *Enterobacteriaceae* (CRE) are emerging extremely drug-resistant pathogens [1]. Enteric strains that harbour carbapenemases, which are plasmid-encoded enzymes, show remarkable epidemic success and have been associated with local, regional and intercontinental dissemination. Such strains consist primarily of *Klebsiella pneumoniae* that produce the serine carbapenemase Klebsiella pneumoniae carbapenemase (KPC) or the metallo-beta-lactamases VIM or NDM-1 [2,3]. These organisms are typically resistant to nearly all available antimicrobial agents [4] and infections by them are associated with an increased risk of mortality [5–7]. Thus, the spread of CRE harbouring carbapenemases is a clinical and public health problem.

Strict contact isolation and physical separation of carriers from non-carriers are key components in containing CRE in acute care hospitals [8]. Relying solely on clinical cultures will not detect the majority of CRE carriers [9]; therefore, active surveillance of patients at high risk of CRE carriage is strongly recommended [4,10]. Sites of CRE carriage include the lower gastrointestinal tract, the oropharynx, skin and urine [11]. The primary surveillance screening site, which has been advocated by the US Centers for Disease Control and Prevention

(CDC) and the European Society of Clinical Microbiology and Infectious Diseases, is the stool or rectal swab [4,10]. Indeed, several studies have demonstrated the role of active surveillance in the control of CRE outbreaks [12,13].

While the implications of having a positive CRE surveillance test are clear in terms of infection control strategy (i.e. asymptomatic carriers should be cohorted with clinically infected patients), the impact of detection of asymptomatic colonization on subsequent infection is unclear. In this study we aimed to determine who among newly identified CRE rectal carriers is prone to have a subsequent clinical specimen with CRE.

## Methods

### Study setting, patient population and definitions

The Tel Aviv Sourasky Medical Centre is a 1200-bed tertiary care teaching hospital in Tel Aviv, Israel. This hospital (like many other Israeli hospitals) has had ongoing CRE outbreaks since 2006 (mainly $bla_{KPC}$ producing *K. pneumoniae* ST258). Cohorting with dedicated staff and strict contact isolation precautions have been enforced for all CRE patients since mid-2007. In addition, screening has been routinely performed for all patients hospitalized in acute or chronic care facilities in the past year and for contacts of newly identified CRE patients [14]. Patients are not cohorted until positive screening results are finalized.

The study population included patients who were identified as CRE carriers by rectal screening tests and had not had prior positive clinical cultures for CRE at the study hospital. Exclusion criteria were age <18 years and affiliation to the obstetrics and gynaecology unit. Data were extracted from the hospital's computerized administrative and laboratory data repositories.

### Study design

A matched case-control study was performed. Cases included all patients with a primary positive CRE rectal test and a subsequent positive CRE clinical culture between 1 May 2007 and 30 April 2009. A clinical culture was defined as any culture other than stool or rectal swab; in case of multiple subsequent CRE clinical cultures, the one most proximal to the positive screening test was assessed. For each case, matched controls were selected at a 1:2 ratio from a pool of patients with a primary positive CRE rectal test and no subsequent positive CRE clinical cultures. Matching was based on (i) calendar time (month/year) of the primary positive CRE rectal test; (ii) whether detection of primary CRE rectal carriage was upon admission or later during hospital stay (≤48 h or >48 h from hospital admission); and (iii) follow-up time, defined as the time-at-risk to develop positive clinical samples after the positive screening test (i.e. controls had to have at least the same follow-up time as their matched case and were censored when reaching the same follow-up time as their matched case).

### Data collection

Data were extracted from the patients' medical records and from a hospital computerized database according to a pre-prepared questionnaire. Three possible predictors of subsequent positive CRE clinical specimens were measured as continuous variables: age, days in hospital in the 30 days before screening, and days in hospital during the follow-up period. The following possible predictors were measured as categorical variables: sex, admission from a long-term care facility or from another hospital, co-morbid conditions (diabetes mellitus (DM), cardiovascular, renal, lung or neurological disease, malignancy, immunodeficiency, skin ulcers), debilitated functional state, hospital unit at the time of screening, contact with the healthcare system 30 days before screening (hospitalization ≥2 days, mechanical ventilation, exposure to antibiotics >1 day) and during the follow-up period (hospitalization ≥2 days and >7 days, admission to the intensive care unit (ICU), mechanical ventilation, exposure to antibiotics (categorized by class) >1 day, surgery, and presence of invasive devices including permanent urinary catheter, central venous catheter (CVC), enteral feeding tube, drain and endotracheal tube). Two reviewers independently determined whether CRE clinical specimens represented infection or colonization based on definitions outlined by the CDC [15]; in cases of disagreement, a third reviewer was consulted.

### Microbiological methods

Rectal swabs were streaked onto selective MacConkey agar plates supplemented with 1 mg/L imipenem. Growing colonies were identified to the species level and tested for carbapenem resistance using the Vitek 2 system (bioMerieux, Marcy l'Etoile, France) and Etest for validation (AB Biodisk, Solna, Sweden). This method has been determined to be adequately sensitive (85%) and specific (94%) for screening purposes [16]. Enterobacteriaceae colonies were also tested for $bla_{KPC}$ using PCR. A CRE screening test was defined as positive if either a CRE isolate was identified and/or $bla_{KPC}$ was detected. Clinical specimens were processed in accordance with the CLSI guidelines [17] and isolates were identified using the Vitek 2 system.

### Statistical analysis

The association between presumptive predictors and subsequent CRE clinical specimens for the matched case-control

triplets was first examined by means of matched bivariate analysis using stratified Cox regression with constant follow-up time. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated. Variables with a p value of ≤0.10 were entered into a multivariate conditional logistic regression analysis using Cox regression with constant follow-up time. The final model was constructed based on a forward stepwise method with the likelihood ratio test, in which variables with a p value ≤0.05 were retained. SPSS statistics for Windows, PASW version 18.0, was used for the analyses.

## Results

### Patient characteristics

Between 1 May 2007 and 30 April 2009 there were 502 newly identified CRE rectal carriers (out of 14 715 unique specimens from 10 040 patients). Of these 502, 44 (8.8%) developed subsequent positive clinical cultures with CRE; these 44 were defined as study cases. Among them, 12 patients were screened within 48 h of hospital admission and 32 were screened later during hospitalization. The time interval between screening and subsequent clinical specimens ranged from 3 to 27 days (mean 11 ± 7 days). Eighty-eight newly identified CRE rectal carriers with no positive clinical specimens for CRE who fulfilled matching criteria were randomly selected as controls. Patients' ages ranged from 26 to 101 years (mean 76 ± 13.6 years) and 52% were male.

### Microbiological characteristics

*Klebsiella pneumoniae* was the predominant CRE isolate identified by rectal screening (43/44 cases (97.7%) and 79/88 controls (89.8%)). Other CRE isolates included *Escherichia coli* (*n* = 5), *Enterobacter* spp. (*n* = 2) and *Citrobacter freundii* (*n* = 1), all among controls. Ninety-two per cent of the tested CRE isolates were $bla_{KPC}$ positive. Two patients (one case and one control) with no identified CRE isolate in their screening specimen were categorized as CRE carriers because of a positive PCR. *K. pneumoniae* was the only CRE isolate identified in the subsequent clinical cultures. The antimicrobial susceptibility profile of the 174 CRE isolates is presented in Table 1. Susceptibility was low for all agents except gentamicin and colistin.

### Clinical characteristics

Among the 44 cases, 38 (86.4%) were classified as clinically infected with CRE; types of infections included urinary tract infection (*n* = 16, 42.1%), bloodstream infection (*n* = 8, 21.1%), pneumonia (*n* = 6, 15.8%), skin and soft tissue infection including surgical site infection (*n* = 5, 13.2%), osteomyelitis including mastoiditis (*n* = 2, 5.2%), and intra-abdominal infection (*n* = 1, 2.6%). The other six CRE clinical cultures (four urine specimens, one penile discharge, and one blood culture drawn from a CVC) were interpreted as colonization.

### Risk factor analysis

Table 2 presents the results of the bivariate analysis of risk factors associated with having a subsequent CRE clinical specimen. Cases were significantly more likely than controls to have a history of DM (43.2% vs. 26.1%, p 0.046). During the month preceding the positive screening test, cases spent fewer days in the hospital (12.7 vs. 17.1, p 0.007) and were less likely to have been hospitalized for 2 or more days (75.0% vs. 88.6%, p 0.026). During the follow-up period, cases were more likely than controls to be hospitalized longer (10.5 days vs. 8.8 days, p 0.095), to be admitted to the ICU (11.4% vs. 2.3%, p 0.054), to have a CVC (20.5% vs. 6.8%, p 0.024), and to receive antibiotics (84.1% vs. 65.9%, p 0.038). Investigation into the classes of antibiotics received during that period revealed that there was significantly greater use of fluoroquinolones and vancomycin among cases than among controls (Table 3).

The multivariate analysis for matched data is presented in Table 4. In this model, admission to the ICU, having a CVC, and receipt of antibiotics (all during the follow-up period) and DM were independent risk factors for subsequent clinical CRE cultures. The variable 'hospitalization in the month preceding the screening test' was not included in the final model because only 16% of study patients were classified as not being hospitalized when the cut-off point was set at 2 or more days; moreover, when different cut-off points were used (7, 10, 14, and 21 days), there was no clear association

**TABLE 1. Antimicrobial susceptibility profile of 174 CRE isolates[a]**

| | AK | GEN | P/T | CAZ | CEF | CIP | LEVO | T/S | COL |
|---|---|---|---|---|---|---|---|---|---|
| Susceptibility rates[b] (%) | 28/174 (16.1) | 148/174 (85.1) | 0/174 (0.0) | 0/174 (0.0) | 2/174 (1.1) | 5/174 (2.9) | 13/174 (7.5) | 13/174 (7.5) | 39/39 (100) |

[a]All isolates were resistant to carbapenems by definition.
[b]Number of susceptible isolates/number of isolates tested.
AK, amikacin; GEN, gentamicin; P/T, piperacillin/tazobactam; CAZ, ceftazidime; CEF, cefepime; CIP, ciprofloxacin; LEVO, levofloxacin; T/S, trimethoprim-sulphamethoxazole; COL, colistin.

**TABLE 2. Bivariate analysis of risk factors associated with a positive clinical specimen for CRE**

| Variable | Mean ± SD or *n* (%) | | OR (95% CI) | p |
|---|---|---|---|---|
| | Clinical sample | No clinical sample | | |
| Demographic | | | | |
| Age (years) | 75.9 ± 15.3 | 76.6 ± 12.8 | | 0.780 |
| Sex (male) | 21 (47.7) | 48 (54.5) | 0.74 (0.34–1.60) | 0.440 |
| Institution[a] | 16 (37.2) | 37 (48.1) | 0.61 (0.27–1.40) | 0.248 |
| Admission unit (survey) | | | | |
| Non-internal medicine | 9 (20.5) | 15 (17.0) | 1.30 (0.48–3.50) | 0.608 |
| ICU | 3 (6.8) | 1 (1.1) | 6.00 (0.62–57.68) | 0.121 |
| Co-morbidities | | | | |
| Cardiovascular disease | 35 (79.5) | 67 (76.1) | 1.23 (0.50–3.05) | 0.652 |
| Diabetes mellitus | 19 (43.2) | 23 (26.1) | 2.29 (1.02–5.17) | 0.046 |
| Renal disease | 15 (34.1) | 19 (21.6) | 2.04 (0.85–4.90) | 0.110 |
| Lung disease | 10 (22.7) | 19 (21.6) | 1.07 (0.44–2.58) | 0.880 |
| Liver disease | 3 (6.8) | 3 (3.4) | 2.38 (0.38–14.97) | 0.355 |
| Neurological disease | 22 (50.0) | 46 (52.3) | 0.89 (0.40–2.00) | 0.786 |
| Malignant disease | 9 (20.5) | 16 (18.2) | 1.15 (0.47–2.80) | 0.758 |
| Immunodeficiency | 3 (6.8) | 12 (13.6) | 0.46 (0.12–1.73) | 0.249 |
| Decubitus ulcer | 2 (4.5) | 4 (4.5) | 1.00 (0.16–6.42) | 1.00 |
| Debilitated functional status | 28 (65.1) | 44 (57.9) | 1.38 (0.64–3.00) | 0.408 |
| Contact with the HCS before survey (30 days) | | | | |
| Any hospitalization (≥2 days) | 33 (75.0) | 78 (88.6) | 0.09 (0.01–0.76) | 0.026 |
| Days in hospital | 12.7 ± 10.7 | 17.1 ± 10.8 | | 0.007 |
| Ventilation | 17 (38.6) | 31 (35.2) | 1.16 (0.55–2.48) | 0.699 |
| Receipt of antibiotics | 35 (79.5) | 67 (76.1) | 1.22 (0.50–2.97) | 0.659 |
| Contact with the HCS after survey | | | | |
| Any hospitalization (≥2 days) | 42 (95.5) | 80 (90.9) | 2.14 (0.43–10.71) | 0.356 |
| Days in hospital | 10.5 ± 6.7 | 8.8 ± 6.2 | | 0.095 |
| Days in hospital >7 | 29 (65.9) | 46 (52.3) | 3.81 (1.03–14.02) | 0.045 |
| ICU stay | 5 (11.4) | 2 (2.3) | 5.00 (0.97–25.77) | 0.054 |
| Ventilation | 21 (47.7) | 28 (31.8) | 1.97 (0.92–4.20) | 0.079 |
| Receipt of antibiotics | 37 (84.1) | 58 (65.9) | 2.69 (1.06–6.88) | 0.038 |
| Surgery | 3 (6.8) | 1 (1.1) | 6.00 (0.62–57.68) | 0.121 |
| Instrumentation after survey | | | | |
| Urinary Foley catheter | 26 (59.1) | 42 (47.7) | 1.52 (0.76–3.06) | 0.241 |
| Central venous catheter | 9 (20.5) | 6 (6.8) | 4.65 (1.22–17.65) | 0.024 |
| Enteral feeding tube | 7 (15.9) | 19 (21.6) | 0.66 (0.24–1.81) | 0.420 |
| Endotracheal tube | 3 (6.8) | 7 (8.0) | 0.86 (0.22–3.32) | 0.823 |
| Drain | 1 (2.3) | 1 (1.1) | | NA |

ICU, intensive care unit; HCS, healthcare system.
[a]Admission from a long-term care facility or another hospital.

**TABLE 3. Case-control comparison of antibiotic use by class**

| Antibiotic class | No. (%) of patients | | OR (95% CI) | p |
|---|---|---|---|---|
| | Clinical sample | No clinical sample | | |
| Penicillins | 14 (31.8) | 18 (20.5) | 1.81 (0.78–3.72) | 0.178 |
| Cephalosporins | 13 (29.5) | 26 (29.5) | 1.00 (0.42–2.38) | 1 |
| $\beta$-lactam $\beta$-lactamase inhibitor combinations | 2 (4.5) | 4 (4.5) | 1.00 (0.16–6.42) | 1 |
| Carbapenems | 6 (13.6) | 11 (12.5) | 1.10 (0.39–3.06) | 0.860 |
| Fluoroquinolones | 15 (34.1) | 12 (13.6) | 3.68 (1.39–9.74) | 0.009 |
| Aminoglycosides | 5 (11.4) | 9 (10.2) | 1.12 (0.36–3.49) | 0.845 |
| Vancomycin | 11 (25.0) | 9 (10.2) | 2.78 (1.06–7.27) | 0.037 |
| Metronidazole | 15 (34.1) | 19 (21.6) | 1.79 (0.83–3.89) | 0.139 |
| Colistin | 5 (11.4) | 6 (6.8) | 1.67 (0.51–5.46) | 0.399 |
| Other antibiotic classes | 7 (15.9) | 13 (14.8) | 1.10 (0.39–3.08) | 0.860 |

between this variable and the outcome measure. Substitution of individual antibiotic classes for the covariate 'antibiotics' revealed that receipt of fluoroquinolones was an independent predictor of subsequent CRE clinical specimens.

Subgroup analysis of the 38 cases who were classified as having a clinical infection with CRE and their matched controls yielded similar results, except that metronidazole use (in addition to fluoroquinolone use) was also identified as an independent risk factor for subsequent CRE clinical specimens (OR, 3.04; 95% CI, 1.13–8.16; p 0.027).

**TABLE 4. Multivariable analysis of risk factors associated with subsequent clinical cultures with CRE**

| Variable | OR (95% CI) | p |
|---|---|---|
| ICU stay[a] | 7.45 (1.32–42.13) | 0.023 |
| Central venous catheter[a] | 5.70 (1.39–23.39) | 0.016 |
| Receipt of antibiotics[a] | 3.32 (1.14–9.69) | 0.028 |
| Receipt of a fluoroquinolone[a] | 3.04 (1.07–8.68) | 0.037 |
| Diabetes mellitus | 2.79 (1.11–7.04) | 0.030 |

ICU, intensive care unit.
[a]Variables refer to the follow-up period after the positive rectal screen test. Omnibus test for both models (i.e. including the variable 'antibiotics' or 'fluoroquinolones': p <0.01).

## Discussion

Colonization with potential pathogens is almost always a prerequisite for the development of nosocomial infections [18]. However, only a minority of colonized patients eventually develops clinical infection [19,20]. This proportion is deter-

mined by various factors, including pathogen virulence and host defence mechanisms, medical procedures, and exposure to antibiotics. Identification of the risk factors for subsequent infections among colonized patients is important; it may promote control of modifiable risk factors and can be used to direct empirical antimicrobial therapy when necessary.

In this study we have addressed progression to infection among patients with CRE rectal carriage. We used isolation from clinical sites as a marker for infection and found that 8.8% of carriers later had a positive CRE clinical specimen, of which most (86%) represented true infection. Our results are very similar to a recently published study by Borer *et al.*, also from Israel, in which 9% of carriers of carbapenem-resistant *K. pneumoniae* developed clinical infection [21]. We found the following variables to be predictors of CRE isolation in clinical specimens among carriers: admission to the ICU, having a CVC, exposure to antibiotics and DM.

ICU-acquired infections by multidrug-resistant bacteria are important complications of the treatment of critically ill patients [22]. Moreover, the ICU has been associated with subsequent clinical infections among patients colonized with drug-resistant bacteria, such as MRSA [19]. Suggested predisposing factors include: (i) patients' underlying health impairments; (ii) the acute disease process; (iii) the frequent use of invasive devices; and (iv) the frequent use of broad-spectrum antibiotics [22]. ICU stay and other indicators of severe illness, such as mechanical ventilation or APACHE score, have also been identified as risk factors for CRE isolation [5,6,23–26]. Our study clarifies the timing of the ICU stay in the pathogenesis of CRE infection; namely, that once rectal colonization has occurred, the ICU setting promotes the transition to clinical infection.

In addition to the role of the ICU, other findings in our study suggest that the transition from CRE rectal carriage to clinical infection is most likely to occur in the context of acute illness. First, patients with subsequent CRE clinical cultures had fewer days of hospitalization and a lower likelihood of any hospitalization before screening. Second, the time interval between screening and clinical specimen was relatively short (<30 days in all cases and <14 days in 75% of cases), indicating that as time passes, the risk of progression from carriage to infection decreases.

Antibiotic pressure is an important determinant of the development and spread of antibiotic-resistant bacteria [27] It is also among the few modifiable risk factors for antibiotic resistance. Data from previous studies have been very supportive of the association between CRE colonization or infection and prior exposure to antibiotics; inconsistent definitions of 'prior' and 'exposure' might explain at least some of the discrepancy in results when specific antibiotic classes are considered [5,6,23–26,28–30]. In the present study we found that the period after rectal carriage had been determined was the time frame in which exposure to antibiotics increased the risk of developing CRE infection. Regarding specific antibiotic classes, we identified exposure to fluoroquinolones and to metronidazole to be associated with subsequent CRE clinical infection. The clinical implication of our findings is that antibiotic therapy, and specifically fluoroquinolones and metronidazole, should be used with caution for CRE carriers.

Our study has several limitations. First, study subjects were identified and classified based on microbiological data solely from the study hospital. Second, clinical samples were taken based on clinical judgement; it is possible that some controls were misclassified because cultures were not taken, which would bias the ORs toward the null hypothesis. Third, patients might have acquired CRE at different time-points before detection by the rectal screening test; therefore, the period at risk in the study may not represent the entire period at risk. We believe that this bias is not important in our study; if it existed, it would be relevant only to the minority of patients who were screened upon hospital admission, and not to the majority who were screened during hospitalization (following contact with an index case). Fourth, the study was conducted in Israel, a region with ongoing outbreaks of KPC-producing CRE (mostly *K. pneumoniae*). The risk factors identified in the present study are relevant to regions with endemic/ongoing outbreaks of CRE harbouring $_{bla}$KPC, but may not be generalizable to other settings with different resistance mechanisms. Other limitations of this study are its retrospective nature and the relatively small sample size, which might have prevented identification of other predictors of subsequent CRE clinical specimens, particularly receipt of other antibiotic classes.

At a time when controlling the spread of CRE is becoming increasingly complicated and mandates surveillance of high-risk individuals, it is important to identify those carriers at risk of developing clinical cultures with CRE. Attention to antimicrobial stewardship could prevent the progression from CRE carriage to infection.

## Acknowledgements

We thank Elizabeth Temkin for her valuable input.

## Transparency Declaration

This work was supported in part by the European Commission Research grant FP7: SATURN impact of Specific Anti-

biotic Therapies on the Prevalence of Human Host Resistant Bacteria Grant No 241796. The authors have no relationship (commercial or otherwise) that may constitute a dua or conflicting interest.

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